ORIGINAL ARTICLE

A single centre cohort experience with a new once daily antiretroviral drug

J Stebbing, M Bower, P Holmes, B Gazzard, M Nelson

Postgrad Med J 2006;**82**:343–346. doi: 10.1136/pmj.2006.044867

See end of article for authors' affiliations

Correspondence to: Dr M Nelson, Department of HIV Medicine, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK; Mark.Nelson@Chelwest.nhs.uk

Submitted 3 January 2006
Accepted February 2006

Background: Atazanavir, an azadipeptide protease inhibitor (PI) with once daily dosing, a lack of insulin resistance, lipid increase, and gastrointestinal toxicities, is approved in combination with other antiretrovirals for the treatment of patients infected with HIV. Unboosted atazanavir is also used in highly active antiretroviral therapy (HAART) naive patients.
Methods: The study prospectively followed up an established cohort of patients who received atazanavir, and for whom one year of follow up data were available.
Results: It was found that use of atazanavir in intent to treat and on treatment analyses, maintained and led to virological suppression and increases in CD4 count in both PI naive and experienced patients. Virological failure occurred in 7% of patients and the main toxicity was hyperbilirubinaemia, which led to treatment withdrawal in 2%. Its efficacy and safety profile was similar to that seen in previous randomised studies investigating its use.
Conclusions: These data should provide reassurance for clinicians wishing to introduce a new antiretroviral into an established cohort.

Despite its obvious success in reducing morbidity and mortality,[1 2] limitations of HAART includes adverse effects, drug-drug interactions, potency, and durability issues and a high pill burden associated with poor compliance.[3–5] Once daily HAART, especially with protease inhibitors (PIs), provides a strategy that should increase adherence and increase the probability of therapeutic success.[6–8]

Atazanavir sulphate (formerly BMS-232632), a bis(L-tert-leucine) derivative, has an elimination half life of seven hours and a pharmacokinetic profile that supports once daily dosing when taken with food.[9–12] Phase 2 clinical trials showed long term potency, safety, rapid viraemic suppression, and durable increases in CD4 counts in both antiretroviral naive[13 14] and experienced patients.[15 16] Large randomised studies have confirmed its antiretroviral and immunological effects,[17] and shown that these effects are similar to other established PIs such as nelfinavir,[18] lopinavir/ritonavir.[19] Its main toxicity has been mild jaundice not associated with hepatotoxicity but secondary to unconjugated hyperbilirubinaemia (attributable to inhibition of UDP glucuronyltransferases), which rarely leads to treatment withdrawal.[20 21]

Compared with other PIs, it has significantly less in vitro effects on glucose transport and is thought to contribute less to insulin resistance.[22] Use of PI based HAART regimens can also result in dyslipidaemia in a significant proportion of patients and such an increase is thought to result in an increase in 10 year coronary risk.[23] Accordingly, minimising dyslipidaemia associated with HAART probably preserves life expectancy.[24 25] Atazanavir has not however been associated with clinically relevant increases in total cholesterol, fasting low density lipoprotein cholesterol or fasting triglyceride concentrations.[26]

At the Chelsea and Westminster Hospital, London, UK, we have prospectively followed up a cohort of patients who received atazanavir since 31 May 2004. We wished to establish their clinical experience, according to their previous PI exposure.

METHODS

The Chelsea and Westminster HIV cohort is the largest single cohort in Europe and data are routinely collected on the patients who attend. HIV positive patients are seen at regular intervals for clinical assessment, trial follow up, and immunological assessments. The HAART era started on 1 January 1996 at this institution and many others and HAART is defined as three or more antiretrovirals, in accordance with published guidelines.[27] We included all patients here who were given atazanavir before 31 May 2004, to ensure that the data we present had more than one year follow up.

RESULTS AND DISCUSSION

We found that giving atazanavir in a well established cohort of patients receiving HAART was safe and effective. A total of

Table 1 Drugs switched to atazanavir

Drug	Number of patients
PIs	
LPV/RTV	34
SQV/RTV	22
NFV	4
RTV	4
IDV/RTV	3
IDV	2
SQV	1
NRTIs	
ABC/DDI	1
AZT/ABC	1
D4T/DDI	1
NNRTIs	
EFV	38
NVP	2

PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; LPV/ RTV, lopinavir/ritonavir; SQV, saquinavir; NFV, nelfinavir; IDV, indinavir; ABC/DDI, abacavir/didanosine; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; NVP, nevirapine.

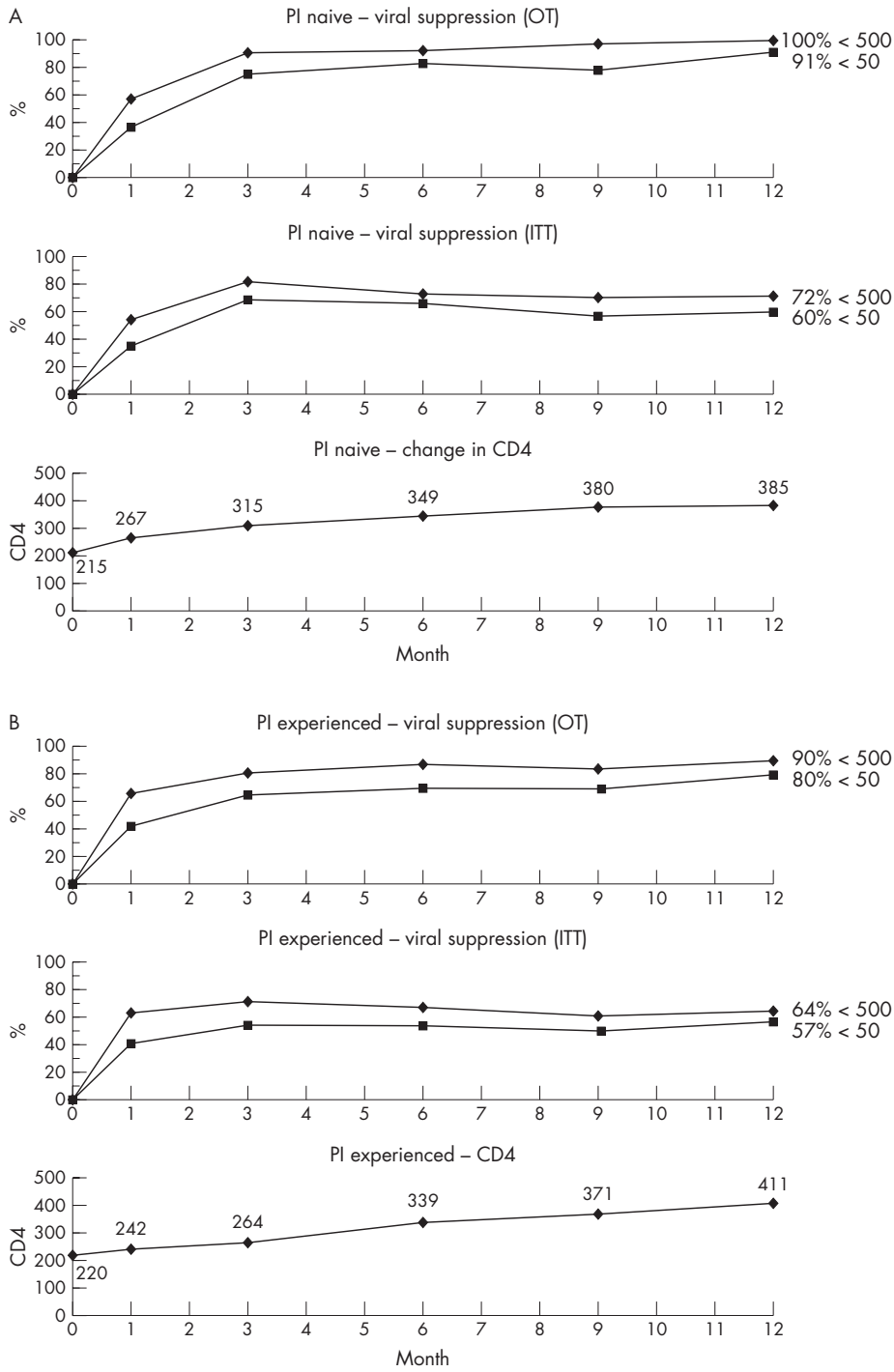

Figure 1 (A) Viral suppression (on treatment and intent to treat) and change in CD4 count in PI naive patients. (B) Viral suppression (on treatment and intent to treat) and change in CD4 count in PI experienced patients.

5873 HIV1 infected patients have been followed up in the HAART era and of these, 241 patients were given atazanavir, comprising 4.1% of the total cohort. From the 241 atazanavir exposed patients, 231 patients (95.8%) received atazanvir (300 mg daily) boosted with ritonavir (100 mg daily) and the remaining 10 received atazanavir alone (400 mg daily).

A total of 113 patients (46.8%) switched to atazanavir from other antiretrovirals (table 1). Of the 241 patients, 76 (31.5%) switched to atazanavir secondary to an adverse drug reaction with a previous antiretroviral, nine (3.7%) switched because of adherence issues, and a further 28 after the premature end of a local efavirenz based trial.

Figure 1 shows the changes in viral load (intent to treat and on treatment) and CD4 count in both the PI naive (fig 1A) and experienced (fig 1B) patients. For PI naive patients in an intent to treat analysis, viral suppression for <500 copies/ml and <50 copies/ml, occurred in 72% and 60% of patients at one year respectively. For PI experienced patients in an intent to treat analysis, viral suppression for <500 copies/ml and <50 copies/ml, occurred in 90% and 57% of patients at one year respectively. The mean CD4 count rise between PI naive and experienced patients showed no significant increases.

Figure 2 shows the decline in viral load in patients who were and were not PI experienced over one year. While PI

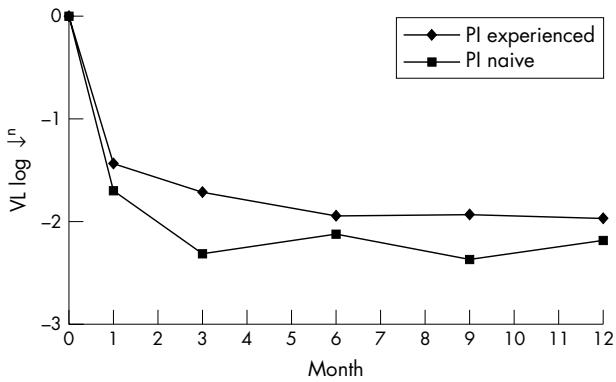

Figure 2 Change in viral load in PI experienced and naive patients over 12 months.

naive experienced patients experienced a greater fall in viral load, no significant differences were seen between these two groups. Switching to atazanavir when the viral load was <50 copies or <500 copies/ml led to continued viral suppression for a year, in both an intent to treat and on treatment analysis (fig 3).

Table 2 shows the changes in cholesterol over 12 months of follow up and shows that the proportion of patients with a total cholesterol greater than 6.5 mmol/l decreased over time while the average cholesterol showed a sustained decrease.

Figure 4 shows the main toxicity previously seen in other studies, unconjugated hyperbilirubinaemia. A small increase in bilirubin was seen over the 12 month period, supporting retrospective data that has evaluated atazanavir related bilirubin increase as an adherence marker.[28]

There were 17 virological failures and we found that the mutations 10F/I, 84V, and 90M are prevalent in resistant patients, as shown by other data.[29] A total of 47 patients stopped atazanavir because adherence or lost to follow up issues (20 patients), virological failure (9 patients), toxicity (9 patients), a structured treatment interruption (4 patients), acute hepatitis C (1 patient), patient request (1), and never taking the drug (1). Of the nine patients who stopped taking atazanavir because toxicity, four stopped because of jaundice,

Table 2 Changes in cholesterol over 12 months of follow up. The proportion of patients with a raised total cholesterol (TC>6.5 mmol/l) is shown.

Month	Cholesterol (mmol/l)	TC >6.5 (%)
0	5.1	15
1	−0.2	11
3	−0.3	8
6	−0.2	8
9	−0.1	5
12	−0.3	9

two because of diarrhoea, one because of depression, one because of a flare of hepatitis C, and one because of an abacavir hypersensitivity reaction in their HAART regimen. A total of four patients died, one because of to bacterial pneumonia, one because of Hodgkin's disease, and one because of progressive multifocal leucencephalopathy.

While these data are not randomised and do not show long term durability or potency, in a prospective cohort of 241 patients who took atazanavir with one year of follow up data, we show that (1) atazanavir was well tolerated with few cases of virological failure, (2) its use was successful in patients who were PI naive and experienced, (3) switching to atazanavir when the viral load was <50 copies/ml led to continued viral suppression, (4) cholesterol concentrations decreased in patientss receiving atazanavir, (5) the major adverse event was mild hyperbilirubinaemia, which rarely led to treatment cessation, and (6) failure with ritonavir/atazanavir was not associated with the development of resistance mutations. Although some may consider that the intent to treat data were disappointing, it is important to note that a number of patients who stopped atazanavir were lost to follow up, a problem with prospective cohort studies in general.

Drug side effects and patient reported symptoms are the foremost variables predictive of non-adherence to HAART.[30] Future HIV standard of care will emphasise the use of once daily therapies, especially as HAART penetrates the under-developed world.[31]

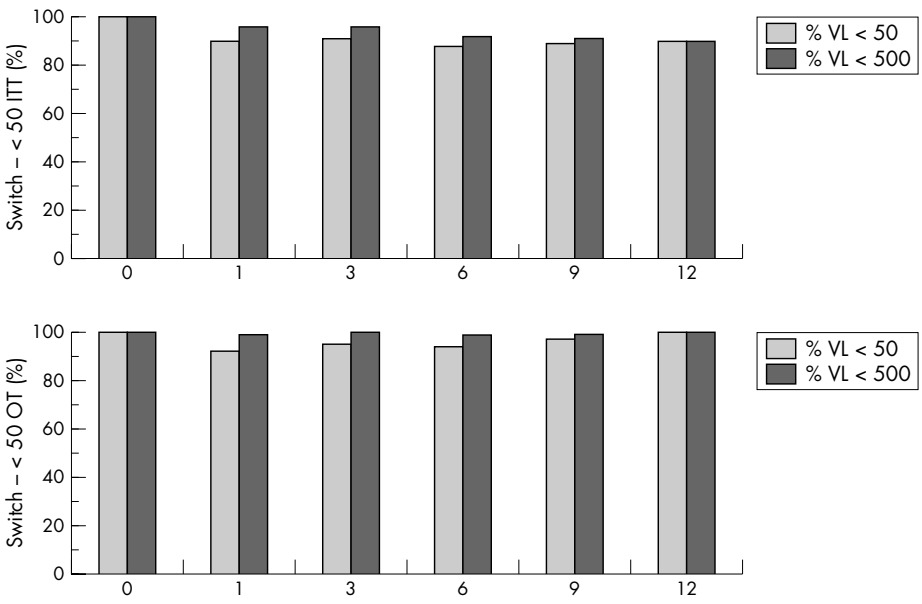

Figure 3 Viral suppression over one year in patients with previously suppressed viraemia.

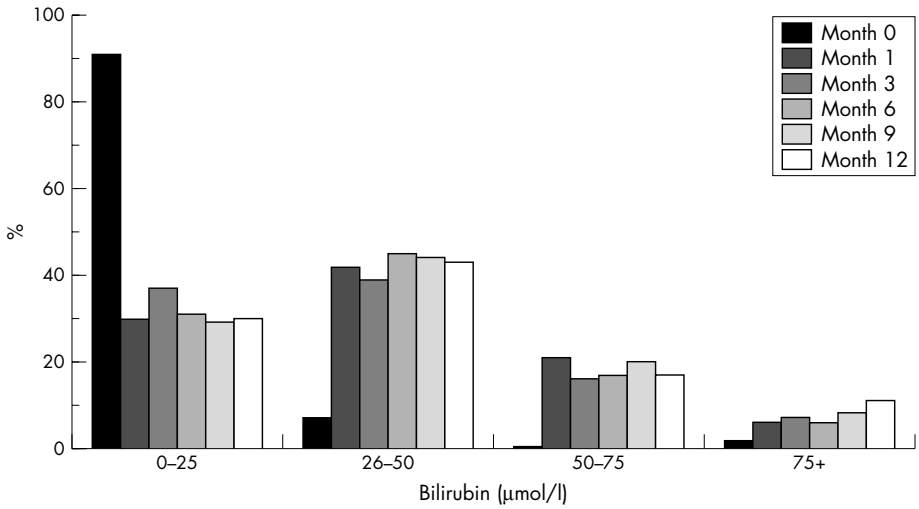

Figure 4 Incidence of hyperbilirubinaemia.

Authors' affiliations

J Stebbing, M Bower, P Holmes, B Gazzard, M Nelson, Department of HIV Medicine, Chelsea and Westminster Hospital, London, UK

Funding: none

Conflict of interest: the authors have received honorariums from Bristol Myers Squib for lecturing and consultancy work.

REFERENCES

1 **Palella FJ Jr**, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;**338**:853–60.
2 **Sterne JA**, Hernan MA, Ledergerber B, *et al.* Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005;**366**:378–84.
3 **Carpenter CC**, Cooper DA, Fischl MA, *et al.* Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2000;**283**:381–90.
4 **Portsmouth S**, Stebbing J, Gazzard B. Current treatment of HIV infection. *Curr Top Med Chem* 2003;**3**:1458–66.
5 **Osterberg L**, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487–97.
6 **Hammer SM**. Increasing choices for HIV therapy. *N Engl J Med* 2002;**346**:2022–3.
7 **Dando TM**, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004;**64**:2075–82.
8 **Back DJ**, Burger DM, Flexner CW, *et al.* The pharmacology of antiretroviral nucleoside and nucleotide reverse transcriptase inhibitors: implications for once-daily dosing. *J Acquir Immune Defic Syndr* 2005;**39**(suppl 1):S1–23.
9 **Raja A**, Lebbos J, Kirkpatrick P. Atazanavir sulphate. *Nat Rev Drug Discov* 2003;**2**:857–8.
10 **Le Tiec C**, Barrail A, Goujard C, *et al.* Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* 2005;**44**:1035–50.
11 **Seminari E**, Guffanti M, Villani P, *et al.* Steady-state pharmacokinetics of atazanavir given alone or in combination with saquinavir hard-gel capsules or amprenavir in HIV-1-infected patients. *Eur J Clin Pharmacol* 2005;**61**:545–9.
12 **Winston A**, Bloch M, Carr A, *et al.* Atazanavir trough plasma concentration monitoring in a cohort of HIV-1-positive individuals receiving highly active antiretroviral therapy. *J Antimicrob Chemother* 2005;**56**:380–7.
13 **Witherell G**. BMS-232632 (Novartis/Bristol-Myers Squibb). *Curr Opin Invest Drugs* 2001;**2**:340–7.
14 **Sanne I**, Piliero P, Squires K, *et al.* Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr* 2003;**32**:18–29.
15 **Sax PE**. Meeting notes from the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. Atazanavir in treatment-experienced patients. *AIDS Clin Care* 2003;**15**:78.
16 **Wood R**, Phanuphak P, Cahn P, *et al.* Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or atazanavir. *J Acquir Immune Defic Syndr* 2004;**36**:684–92.
17 **Martinez E**, Arnaiz JA, Podzamczer D, *et al.* Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003;**349**:1036–46.
18 **Murphy RL**, Sanne I, Cahn P, *et al.* Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 2003;**17**:2603–14.
19 **Cohen C**, Nieto-Cisneros L, Zala C, *et al.* Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. *Curr Med Res Opin* 2005;**21**:1683–92.
20 **Rodriguez Novoa S**, Barreiro P, Rendon A, *et al.* Plasma levels of atazanavir and the risk of hyperbilirubinemia are predicted by the 3435C–>T polymorphism at the multidrug resistance gene 1. *Clin Infect Dis* 2006;**42**:291–5.
21 **Zhang D**, Chando TJ, Everett DW, *et al.* In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. *Drug Metab Dispos* 2005;**33**:1729–39.
22 **Noor MA**, Parker RA, O'Mara E, *et al.* The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. *AIDS* 2004;**18**:2137–44.
23 **Grover SA**, Coupal L, Gilmore N, *et al.* Impact of dyslipidemia associated with highly active antiretroviral therapy (HAART) on cardiovascular risk and life expectancy. *Am J Cardiol* 2005;**95**:586–91.
24 **Friis-Moller N**, Sabin CA, Weber R, *et al.* Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;**349**:1993–2003.
25 **Grinspoon S**, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005;**352**:48–62.
26 **Cahn PE**, Gatell JM, Squires K, *et al.* Atazanavir—a once-daily HIV protease inhibitor that does not cause dyslipidemia in newly treated patients: results from two randomized clinical trials. *J Int Assoc Physicians AIDS Care (Chic Ill)* 2004;**3**:92–8.
27 **Yeni PG**, Hammer SM, Hirsch MS, *et al.* Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. *JAMA* 2004;**292**:251–65.
28 **Petersen K**, Riddle MS, Jones LE, *et al.* Use of bilirubin as a marker of adherence to atazanavir-based antiretroviral therapy. *AIDS* 2005;**19**:1700–2.
29 **Vora S**, Marcelin AG, Gunthard HF, *et al.* Clinical validation of atazanavir/ritonavir genotypic resistance score in protease inhibitor-experienced patients. *AIDS* 2006;**20**:35–40.
30 **Ammassari A**, Murri R, Pezzotti P, *et al.* Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 2001;**28**:445–9.
31 **Sande MA**, Ronald A. Treatment of HIV/AIDS: do the dilemmas only increase? *JAMA* 2004;**292**:266–8.